An oscillation of the respiratory control system accounts for most of the heart period variability of chronic heart failure patients

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ABSTRACT
A periodic breathing (PB) pattern is often observed in chronic heart failure (CHF) patients (pts). In order to clarify the role of this abnormal respiratory activity upon heart period variability we investigated, in a group of 20 stable CHF pts (NYHA class II to III, median EF 24 %) showing a PB pattern, 1) whether observed data were consistent with the instability hypothesis of PB and 2) the relationship between this oscillation and the contemporary fluctuations of ventilatory and chemoreceptor activity. Univariate and bivariate spectral analysis were performed on short-term resting recordings of instantaneous lung volume (ILV), instantaneous minute ventilation (IMV), heart period (HP) and arterial O2 saturation at the ear (SpO2). A very low frequency (VLF) oscillation around 0.02 Hz, associated with PB, was observed in all signals and contributed to 75% (23+99) (median (range)) of the HP variability. The coherence between ILV and HP was 0.77 (0.3±0.95) and between SpO2 and HP 0.8 (0.4±0.98). A high coherence was also found between IMV and SpO2: 0.9 (0.6±0.98). The median phase lag between IMV and SpO2 was -21° (-260+156), between ILV and HP -205° (-260±180) and between SpO2 and HP 6° (-26±30). The estimated lung-to-ear circulation time was 24.5 s (12.5±36.5). This study definitely confirms that during PB a common rhythm is shared between the respiratory and cardiovascular regulatory system. Taking into account the error introduced by the measuring process, our results are consistent with the hypothesis that periodic breathing of CHF pts originates from an instability of the feedback control system of ventilation. Hence most of the HP variability of these pts simply reflects the abnormal pattern of respiratory activity.

INTRODUCTION
Clinical studies on short-term (<10 min) heart rate variability often tend to disregard the influence of respiratory activity upon estimated variability indexes. This problem becomes particularly evident when these indexes are measured during different states such as sleep and waking or rest and exercise, or when the subject's breathing pattern is markedly abnormal due to respiratory rhythm disorders. A paradigmatic case of the latter situation is given by severe heart failure patients (pts) who are known to develop the so called Cheyne-Stokes (C-S) respiration frequently [1]. Recently it has also been observed that an oscillatory breathing pattern characterized by a smooth rise and fall in ventilation, without true periodicity of breathing, as observed in chronic heart failure (CHF) patients, is a well defined very low frequency (VLF) peak centered around 0.015 Hz [3]. Despite the technical limitations of the ECG-derived respiratory signal used for the analysis, they also observed a VLF peak in the spectrum of respiratory activity and hypothesized a link between this respiratory oscillation and the corresponding oscillation of heart rate, mediated primarily by the modulation of sympathetic activity. More recently our group, monitoring a true ventilatory signal in a sample of moderate CHF patients without clear signs of C-S respiration and using spectral decomposition techniques, found in most of them a VLF oscillation around 0.02 Hz in the instantaneous tidal volume signal, synchronous with a contemporary oscillation of ventilatory baseline [4]. A dominant oscillation around the same frequency was also observed in the heart period (HP) signal and, most notably, in the great majority of patients it was moderately to highly coherent with the concomitant oscillation of ventilatory activity. Thus we had strong confirmation that the observed phenomenon was a cardiorespiratory oscillation.

In this work a further step towards the clarification of the complex mechanisms responsible for the periodic breathing pattern of CHF patients and for corresponding fluctuations of heart rate will be added by 1) investigating whether observed data are consistent with the classical hypothesis which explains periodic breathing in terms of an instability of the negative feedback control system of respiratory activity [5] and 2) by analyzing, by means of coherence analysis and phase analysis, the relationship between the VLF oscillation of heart period and the contemporary fluctuations of ventilatory and chemoreceptor activity.

METHODS
Subjects and protocol
We recorded 8 min of ECG, instantaneous lung volume by uncalibrated inductance plethysmography (Respitrace) and arterial oxygen saturation (SpO2) by a fast response pulse oximeter with ear probe (Ohmeda Biox 3740) in 52 moderate CHF patients (NYHA class II to III) on stable therapy and without signs and symptoms of heart failure during the last two weeks. None of them had a history of pulmonary or neurologic disease. All recordings were performed at rest in the supine position and during spontaneous respiration. During these recordings 33 patients showed a stable periodic breathing pattern, as ascertained by visual inspection of the respiratory signal and by the appearance of a well defined peak in the range 0.01-0.04 Hz (VLF band) in the power spectrum of the instantaneous minute ventilation signal. To obtain this signal, we first measured the tidal volume in each respiratory cycle and then divided this quantity by the duration of the corresponding cycle. The resulting time series was then interpolated by a cubic spline and resampled at 2 Hz. The same type of interpolation was also applied to the heart period time series, while the lung volume and saturation signals were decimated to have all signals sampled synchronously, as required by subsequent bivariate spectral analysis. Finally, all signals were plotted together and we searched for a 3 minute sub-record with all signals stationary and free from artefacts. Only 20 patients fulfilled these criteria and were admitted to subsequent analysis. Their median age was 51 years (range 29±66 years) and the median ejection fraction was 24 % (range 13±42 %).

Basic Assumptions
In order to assess the consistency of the instability hypothesis of periodic breathing a few simplifying assumptions were made. First it was assumed that periodic breathing is mediated primarily by the peripheral (carotid) controller (i.e. the contribution of the central (medullary) controller is negligible) and that this controller acts almost instantaneously to adjust alveolar ventilation. Second, that there is no phase difference between the O2 and CO2 components of the peripheral controller. Third, it was also supposed that the SpO2 signal is a good approximation of the arterial O2 saturation signal actually sensed by carotid chemoreceptors and that the phase delay between the carotid chemoreceptors and the ear probe is negligible in comparison with the phase delay of the overall control loop. Under these major assumptions an approximate phase shift of the respiratory control loop at the periodic breathing frequency can be obtained by measuring the phase delay between ventilatory activity (i.e. the instantaneous minute ventilation signal) and oxygen saturation at the ear (i.e. the SpO2 signal). To meet the Nyquist criterion for instability this phase delay should be 180°.
cycle and with a smoothing of high frequency components by the O2 saturation signal. The heart period signal substantially fluctuates in phase with the O2 saturation, but is out of phase (i.e. it has 180° phase shift) with respect to the VLF component of the lung volume and minute ventilation signals. Notice that, although the lung volume signal shows a pronounced swing at the respiratory frequency, the corresponding high frequency component of the heart period is dramatically reduced in comparison with the VLF oscillation. Consequently, corresponding spectra of all signals (Fig. 1a-h), except the lung volume, are dominated by a peak around 0.03 Hz.

**Figure 1** - Example of recorded signals and corresponding autospectra. (a), (e): instantaneous lung volume; (b), (f): instantaneous minute ventilation; (c), (g): O2 saturation; (d), (h): heart period. A.U.: Arbitrary Units.

**Data Analysis**

Spectral analysis of recorded time series was performed following the autoregressive approach (Burg algorithm). Model order was interactively selected by finding the best overlap between the autoregressive spectral estimate and that obtained by the Blackman-Tukey approach (Parzen window with bandwidth = 0.015 Hz) [6]. Bivariate spectral analysis of minute ventilation versus O2 saturation, O2 saturation versus heart period and lung volume versus heart period was performed using the Square-Root Normalized MEM algorithm [7]. The phase delay between 2 signals at the PB frequency was estimated only if 1) a well defined peak in the VLF band was found in the autospectrum of both signals and 2) the magnitude square coherence function around this peak was > 0.5 (to ensure the statistical reliability of the estimate). The periodic breathing frequency was defined as the mean of central frequencies of the VLF component of instantaneous minute ventilation and arterial saturation signals. By convention the phase delay between 2 signals S1 and S2 is negative if S1 leads.

On the signal sequences of saturation and minute ventilation we also estimated by a computer assisted visual technique the so called lung-to-ear circulation time (LECT) [8]. Although the name of this parameter strictly refers to the pure circulatory delay from the lungs to the ear, it actually measures the time delay from changes of ventilatory activity to the appearance of corresponding gas tension changes at the ear probe of the pulse oximeter.

Data are reported as median (range).

**RESULTS**

A representative example of the set of recorded signals and of corresponding autospectra is given in Fig.1a-h. A marked cyclic modulation of tidal volume with alternating phases of hyperventilation and shallow breathing, characteristic of periodic breathing, can be noticed in the lung volume signal. The minute ventilation signal shows a clear oscillatory pattern which is reproduced with a time delay of about half of a periodic breathing.}

<table>
<thead>
<tr>
<th>VLF central frequency (Hz)</th>
<th>VLF relative power (%)</th>
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<tbody>
<tr>
<td>ILV 0.023 (0.012-0.038)</td>
<td>38 (9-87)</td>
</tr>
<tr>
<td>IMV 0.023 (0.015-0.036)</td>
<td></td>
</tr>
<tr>
<td>SpO2 0.021 (0.012-0.032)</td>
<td></td>
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<tr>
<td>HP 0.020 (0.011-0.031)</td>
<td>75 (23-99)</td>
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Figure 2 - Coherence function (solid line) and phase spectrum (dashed line) for the signals of Fig. 1. (a): instantaneous minute ventilation (IMV) versus O2 saturation (SpO2); (b): O2 saturation versus heart period (HP); (d): instantaneous lung volume (ILV) versus heart period.

Twelve out of the 20 patients analyzed showed a periodic breathing pattern without apneas between the hyperventilation phases. Five patients had clear C-S respiration. In the remaining 3 patients we observed both apneas or hypopneas between the hyperventilation phases. All patients showed a VLF oscillation in the arterial O2 saturation signal. Descriptive statistics of spectral parameters for the overall patient group are given in Table 1.
The VLF component associated with periodic breathing is centered around 0.02 Hz and shows a slight increase in the respiratory signals compared to others. We explain this increase as the consequence of the broader shape of the VLF peak of ventilatory activity signals. The VLF component contributed predominantly to the overall variability of heart period with a median value of 75%. Conversely, it contributed only 38% to the overall variability of the lung volume signal.

We found a high coherence at the VLF peak between minute ventilation and arterial O\textsubscript{2} saturation (0.9 (0.6-0.98)). Nineteen out of 20 pts showed a coherence >> 0.5 between O\textsubscript{2} saturation and heart period (0.8 (0.4-0.98)) as well as between lung volume and heart period (0.77 (0.3-0.95)). Hence, these data provide further evidence that in patients with a periodic breathing pattern a more general cardiorespiratory rhythm is present.

The median phase lag between minute ventilation and O\textsubscript{2} saturation was -211° (-240°-156°). In all pts it was always possible to obtain a close overlap between the minute ventilation and saturation signals after having shifted the latter backward (i.e. anticipated) about half a cycle of the periodic breathing oscillation. The estimated LECT was 24.5 s (12.5-36.5 s), a value in good agreement with the prolonged circulatory delay characteristic of CHF pts and with previously published data [8]. The ratio between the cycle length of periodic breathing and the LECT was 1.85 (1.5-2.6).

The median phase delay between saturation and heart period and between lung volume and heart period was 0° (-260°-30°) and -205° (-260°-180°) respectively, indicating that, as observed in the example of Fig. 1, heart period decreases during the increasing phase of ventilation and falling phase of saturation.

**DISCUSSION**

The analysis of heart rate variability has been often used in recent years as a noninvasive tool to investigate the autonomic control of the cardiovascular function of heart failure patients [9]. Most of these studies, however, either do not consider respiratory activity at all or use inadequate equipment to monitor ventilation. Periodic breathing is a common respiratory pattern in clinically stable chronic heart failure patients with mild to moderate symptoms and poor left ventricular function [2]. In our population of hospitalized patients (NYHA class II to III), about 60% of subjects show a periodic breathing pattern during short-term resting recordings. A sample of these patients having high quality recordings was admitted to this study. Using advanced spectral analysis techniques we have provided strong evidence that most (75%) of the heart period variability observed in these subjects is due to a very low frequency oscillation associated with periodic breathing activity.

A VLF oscillation of the arterial O\textsubscript{2} saturation signal highly coherent with the concomitant oscillation of minute ventilation has also been observed in all patients. The median phase lag between the two signals was -211°, that is about 31° in excess of the theoretical phase lag of 180° required for the respiratory control system to become unstable and generate a self-sustained oscillation. Assuming a pure sinusoidal periodic breathing, this corresponds to an extra circulatory delay of about 3.8 s (median value of individual data).

Since we were not actually measuring the oxygen saturation at the chemoreceptor site but at a greater distance from the lungs and taking into account that the pulse oximeter introduces an intrinsic processing delay of about 1.5 s, the observed extra phase lag seems mostly justified by pure measurement error. Hence, under the assumptions previously defined, our findings are consistent with the hypothesis that the periodic breathing pattern observed in chronic heart failure patients originates from an instability of the feedback control system of ventilation.

A more empirical confirmation of the instability hypothesis of periodic breathing can also be found in the ratio of 1.85 between the period of the respiratory oscillation and the LECT parameter. In fact this is an indirect evidence that minute ventilation and O\textsubscript{2} saturation are out of phase.

An important finding of our study concerns the very close link between the VLF component of the heart period variability and the oscillation of arterial O\textsubscript{2} saturation. The two signals appeared to be approximately in phase. Taking into account the extra delays introduced by the measurement process of arterial saturation, as described above, this implies a delay of a few seconds between chemoreceptor stimulation and changes in heart rate. It must be pointed out that the observed relationship between saturation and heart period may simply be the consequence of an underlying coupling between respiratory activity and heart period and of the high coherence between ventilation and saturation. However, the very close similarity often seen between heart period and O\textsubscript{2} saturation fluctuations suggests that chemoreceptors might be involved in the genesis of the VLF modulation of the RR interval. Excluding a direct involvement of baroreceptors, as the baroreflex is greatly impaired in CHF patients, further investigations are needed to assess the role of chemoreceptors, lung stretch receptors and central coupling in the interaction between respiration and the cardio-vascular function.

Two main practical implications can be drawn from this study. First, the high prevalence of periodic breathing in CHF patients and the consideration that the physiological parameters responsible for respiratory system instability may change from time to time and from subject to subject, causing a change in the characteristics of the ventilatory pattern, strongly encourage the use of heart rate variability measures as markers of autonomic control in CHF patients without a contemporary assessment of ventilatory activity. Second, the oscillation of the arterial oxygen saturation observed during laboratory recordings should direct the clinician's attention towards a thorough consideration of diurnal phasic falls of O\textsubscript{2} arterial tension in heart failure pts and to their possible role in the prediction of breathing pattern abnormalities and O\textsubscript{2} desaturation during sleep.

**REFERENCES**